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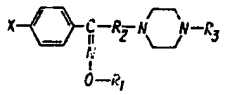
(54) OXIME DERIVATIVES OF HALOPHENYL PIPERAZINYL-ALKYL KETONES AND METHODS FOR THEIR PREPARATION

(71) We, ANDRE BUZAS, a citizen of France of 25 Rue Mignotte, Bievres, Essonne, France, and LES LABORATOIRES BRUNEAU ET CIE, a French Body Corporate, of 17 rue de Berri, Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to oxime derivatives of pharmaceutical utility and their preparation.

The invention provides compounds of the formula:



(I)

in which X represents a halogen atom, preferably chlorine or fluorine, R_1 represents a lower aliphatic hydrocarbyl group, a lower aliphatic hydrocarbyl group substituted by a tertiary amino radical, an alkyl-carbonyl radical, or an aralkyl-carbonyl, an aralkenyl-carbonyl, a phenyl-carbonyl, a furyl-carbonyl, or a pyridyl-carbonyl radical, optionally substituted by up to 3 radicals chosen from halogen atoms and alkyl and alkoxy radicals, the said alkyl and alkenyl radicals each containing a maximum of 8 carbon atoms, R_2 represents a linear or branched, aliphatic group of 1 to 3 carbon atoms and R_3 represents an arylaliphatic or aromatic group (the nitrogen atom of the piperazine ring being attached to an aromatic carbon atom when R_3 is an aromatic group), and their pharmaceutically acceptable acid addition salts. Especially valuable compounds are those in which R_1 is alkyl, alkenyl, alkynyl, dialkylaminoalkyl, morpholinoalkyl, alkanoyl, benzoyl, phenylalkanoyl, phenylalkenoyl, furyl-carbonyl, or pyridyl-carbonyl, the said benzoyl, phenyl, furyl, and pyridyl radicals being unsubstituted or substituted by up to 3 radicals chosen from alkyl, alkoxy, and halogen, and the said alkyl, alkenyl, alkynyl, alkanoyl and alkenoyl radicals each containing a maximum of 8, preferably a maximum of 4, carbon atoms, and R_3 is phenyl or phenylalkyl, each unsubstituted or substituted by up to 3 alkyl, alkoxy or halogen radicals or by methylenedioxy, the said alkyl or alkoxy radicals each containing up to 4 carbon atoms, R_1 can represent, more especially, an allyl, propargyl, β-diethyl-amino-ethyl, β-morpholino-ethyl, di-n-propyl-acetyl, p-n-butoxy-phenyl-acetyl, cinnamoyl, 3,4,5-trimethoxy-benzoyl, 3,4-dichloro-benzoyl, 2,5-dimethyl-3-furyl-carbonyl or 2-chloro-nicotinoyl radical,

R_2 a $—CH_2—$, $—CH(CH_3)—$, $—CH_2—CH_2—$ or $—CH_2—CH_2—CH_2—$ group and R_3 a phenyl or piperonyl radical.

The term "lower aliphatic" as used herein refers to those groups having up to 8 carbon atoms.

Suitable salts are those with pharmaceutically tolerated organic acids such as citric acid, maleic acid or methane-sulphonic acid, and inorganic acids such as hydrochloric acid, nitric acid or sulphuric acid, especially the hydrochlorides and maleates. These salts are crystalline products which are stable and soluble in water.

The compounds of formula I show particularly little toxicity and possess useful

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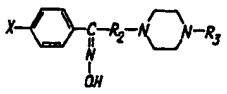
pharmacological activity, especially as analgesic agents, anti-inflammatory agents and musculotropic spasmolytic agents.

According to a feature of the invention the compounds of formula I are made by reacting an oxime of the formula:



(II)

in which X, R_2 and R_3 are as hereinbefore defined, with a compound of the formula:

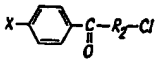
$$R_1—Hal,$$

wherein Hal represents halogen, preferably chlorine, and R_1 is as hereinbefore defined.

When R_1—Hal represents an alkyl, alkenyl or alkynyl halide, the oxime can be used as its sodium or potassium salt and the reaction can be carried out in an alcoholic diluent, e.g. a lower alkanol such as ethanol or tertiary butyl alcohol. When R_1—Hal represents an acid halide, e.g. chloride, the reaction can be carried out in a diluent such as pyridine, and the hydrohalide of the base is then obtained directly.

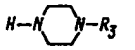
The oximes of the formula II are new compounds. They can be obtained, by the conventional method, by reaction of hydroxylamine, as the hydrochloride, with the corresponding ketone, preferably in an aqueous-alcoholic medium, where necessary in the presence of sodium hydroxide.

The ketone, in its turn, can be prepared by reacting the chlorinated ketone of formula:



(III)

with a piperazine of formula:



(IV)

preferably in an organic diluent such as benzene, toluene or chloroform.

The following Examples illustrate the invention. Examples I and II describe the preparation of certain oximes of the formula II and Examples 1 to 3 illustrate the preparation of compounds of the invention of the formula I.

The characteristics of the oximes are given in Table I and the characteristics of the compounds of formula I are given in Table II.

EXAMPLE I.

Method A

1 - (Hydroxy - imino) - 1 - (4 - fluoro - phenyl) - 4 - (4 - piperonyl - 1 - piperazinyl) - butane (compound IX)

(a) A solution of 440 g. (2 mols) of 4-piperonyl-piperazine in 300 ml. of toluene is added to a solution of 200 g. (1 mol) of 1 - (4 - fluoro - phenyl) - 4-chloro - 1 - butanone in 300 ml. of toluene. 4 g. of finely powdered potassium iodide are added and the mixture is heated under reflux, with stirring, for 6 hours. The piperonyl-piperazine hydrochloride, which has precipitated, is removed and the solvent is driven off *in vacuo*. The residue is crystallised from isopropyl ether. 292 g. (yield 76%) of 1 - (4 - fluoro - phenyl) - 4 - (4 - piperonyl - 1 - piperazinyl) - 1-butanone, m.p. 88—90°C., are obtained.

(b) A solution of 46 g. (1.15 mols) of sodium hydroxide in 100 ml. of water is added to a solution of 96 g. (1.4 mols) of hydroxylamine hydrochloride in 100 ml. of water. A solution of 92 g. (0.42 mol) of the product of (a) in 500 ml. of ethanol is then added and the mixture is heated under reflux, with stirring, for 2 hours. After cooling, the solvent is driven off *in vacuo*. The residue is washed with water and recrystallised from ethanol. 75 g. (yield 78%) of compound IX, m.p. 140°C., are obtained.

EXAMPLE II.

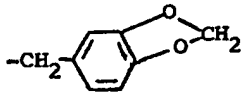
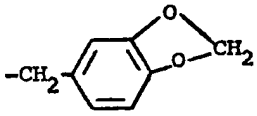
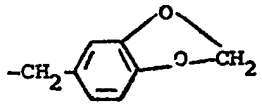
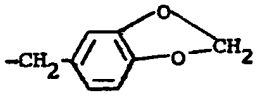
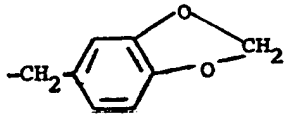
Method B

1 - (Hydroxy - imino) - 1 - (4 - fluoro - phenyl) - 2 - (4 - phenyl-1 - piperazinyl) - ethane (compound III)

5.2 g (0.075 mol) of hydroxylamine hydrochloride are added to a solution of 11.2 g (0.0375 mol) of 1 - (4 - fluoro - phenyl) - 2 - (4 - phenyl - 1 - piperazinyl)-1-ethanone in a mixture of 40 ml. of ethanol and 10 ml. of water. The mixture is heated under reflux for 5 hours, a part of the solvent is evaporated under reduced pressure, and the solution is rendered alkaline with sodium hydroxide solution. The precipitate is filtered off, washed with water, and recrystallised from ethanol. 11 g. (yield 90%) of compound III, m.p. 138°C., are obtained.

The following Table I lists oximes of formula II produced by methods A and B.

TABLE I

Compound No.	X	R_2	R_3	Melting point (°C.)	Method of preparation
I	Cl	$-(CH_2)_3-$		180	A
II	Cl	$-(CH_2)_3-$		138	A
III	F	$-CH_2-$		138	B
IV	F	$-(CH_2)_2-$		160	A
V	F	$-(CH_2)_3-$		190	A
VI	F	$-CH_2-$		174	B
VII	F	$-(CH_2)_2-$		194	A
VIII	F			145	B
IX	F	$-(CH_2)_3-$		140	A

EXAMPLE 1.

1 - (2 - Morpholino - ethoxy - imino) - 1 - (4 - fluoro - phenyl) - 4 - (4 - piperonyl-1 - piperazinyl) - butane and its trimaleate (compound No. 14)

(a) 120 g. (0.3 mol) of compound IX are added gradually, with stirring, to a solution of 7.5 g. (0.33 gram atom) of sodium in 500 ml. of absolute ethanol. The mixture is heated under reflux for 1 hour. After cooling, 48 g. (0.32 mol) of β-morpholino-ethyl chloride are added. The mixture is again heated under reflux for 2 hours. The solvent is driven off *in vacuo*, and the residue is taken up in water and extracted with ether. After drying over sodium sulphate, the solvent is driven off *in vacuo*.

142 g. (yield 93%) of 1 - (2 - morpholino - ethoxy - imino) - 1 - (4 - fluoro-phenyl) - 4 - (4 - piperonyl - 1 - piperazinyl) - butane are obtained.

$n_D^{40} = 1.550$

Rf = approximately 0.8 (thin layer chromatography eluent: 90/10 mixture of methylene chloride and methanol).

Infra-red bands at 920 cm^{-1} and 1,610 cm^{-1}.

(b) A solution of 140 g. (0.273 mol) of the base produced in paragraph (a) in 100 ml. of ethyl acetate is added to a solution of 96 g. (0.82 mol) of maleic acid in 500 ml. of ethyl acetate. The trimaleate which precipitates is filtered off and recrystallised from ethanol. It melts at 200°C.

Infra-red band at 1,675—1,600 cm^{-1}.

Elementary analysis:

	calculated	*found*
C%	55.80	55.58
H%	5.70	5.66
N%	5.59	6.39

EXAMPLE 2.

1 - (2 - Diethylamino - ethoxy - imino) - 1 - (4 - fluoro - phenyl) - 4 - (4 - phenyl-1 - piperazinyl) - butane and its dimaleate (compound No. 9)

(a) A solution of 110 g. (0.68 mol) of 1-phenyl-piperazine in 300 ml. of toluene is added to a solution of 68 g. (0.34 mol) of 1 - (4 - fluoro - phenyl) - 4 - chloro - 1 - butanone in 300 ml. of toluene. 1 g. of finely powdered potassium iodide is added and the mixture is heated under reflux, with stirring, for 6 hours. Phenyl-piperazine hydrochloride, which has precipitated, is separated and the solvent is driven off *in vacuo*. The residue is crystallised from di-isopropyl ether. 85 g. (77% yield) of 1 - (4 - fluoro - phenyl) - 4 - (4 - phenyl - 1 - piperazinyl) - 1 - butanone, m.p. 98°C., are obtained.

(b) A solution of 14.4 g. (0.36 mol) of sodium hydroxide in 100 ml. of water is added to a solution of 30 g. (0.42 mol) of hydroxylamine hydrochloride in 30 ml. of water. A solution of 47 g. (0.144 mol) of 1 - (4 - fluoro - phenyl) - 4 - (4-phenyl - 1 - piperazinyl) - 1 - butanone in 100 ml. of ethanol is then added. The mixture is heated under reflux, with stirring, for 2 hours. After cooling, 1 - (4 - fluoro-phenyl) - 4 - (4 - phenyl - 1 - piperazinyl) - 4 - butanone - oxime (compound V), which has separated out, is filtered off, and washed with water and then ethanol. 43 g. of this oxime (88 % yield), m.p. 190°C., are obtained.

(c) 185 g. (0.54 mol) of 1 - (4 - fluoro - phenyl) - 4 - (4 - phenyl - 1-piperazinyl) - 4 -butanone - oxime are added gradually, with stirring, to a solution of 66 g. (0.6 mol) of potassium tertiary butoxide in 500 ml. of tertiary butyl alcohol. The mixture is heated under reflux for 4 hours. 82 g. (0.6 mol) of β-diethylamino-ethyl chloride are then added. The mixture is heated under reflux for 1 hour. The solvent is driven off *in vacuo* and the residue, having been washed with water, is extracted with ether. After drying over sodium sulphate, the solvent is driven off *in vacuo*. 217 g. of 1 - (2 - diethylamino - ethoxy - imino) - 1 - (4 - fluoro - phenyl)-4 - (4 - phenyl - 1 - piperazinyl) - butane (91% yield) are obtained, $n_D^{40} = 1.546$.

Rf = approximately 0.8 (thin layer chromatography eluent: 90/10 mixture of methylene chloride and methanol)

Infra-red bands at 920 and 1,610 cm^{-1}.

(d) A solution of 217 g. (0.49 mol) of 1 - (2 - diethylamino - ethoxy - imino)-1 - (4 - fluoro - phenyl) - 4 - (4 - phenyl - 1 - piperazinyl) - butane in 200 ml. of ethyl acetate is added to a solution of 172 g. (1.48 mols) of maleic acid in 500 ml. of ethyl acetate. The mixture is left for 24 hours in a refrigerator. The precipitate

of 1 - (2 - diethylamino - ethoxy - imino) - 1 - (4 - fluoro - phenyl) - 4 - (4 -phenyl-1 - piperazinyl) - butane dimaleate is filtered off, m.p. 115°C.
Infra-red band at 1,620 cm^{-1}.

Elementary analysis:

	calculated	*found*
C%	60.85	60.43
H%	6.70	6.76
N%	8.33	8.29

EXAMPLE 3.

1 - (2 - Chloro - nicotinoyloxy - imino) - 1 - (4 - fluoro - phenyl) - 4 - (4-piperonyl - 1 - piperazinyl) - butane hydrochloride (compound No. 26).

A solution of 80 g. (0.45 mol) of 2-chloro-nicotinoyl chloride in 500 ml. of anhydrous pyridine is added slowly, with stirring, to a solution of 150 g. (0.376 mol) of compound IX in 500 ml. of anhydrous pyridine kept at 0°C. At the end of the addition, the mixture is allowed to return to ambient temperature and is kept at this temperature for 12 hours. It is then concentrated *in vacuo* and the residue, which is the desired product, is taken up in ethanol. It melts at 250°C.
Infra-red band at 1,760 cm^{-1}.

Elementary analysis:

	calculated	*found*
C%	58.50	57.95
H%	5.05	5.04
N%	9.75	9.66

The characteristics of the corresponding free base are as follows: $n_D^{40} = 1.420$
Rf=approximately 0.9 (thin layer chromatography eluent: 90/10 mixture of methylene chloride and methanol)
Infra-red bands at 1,750, 1,610 and 920 cm^{-1}.

Data for certain compounds of the invention which have been made by the foregoing methods are given in the following Table II.

TABLE II

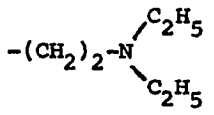
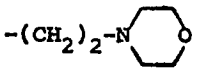
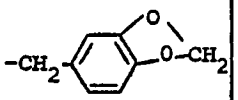
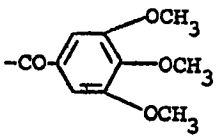
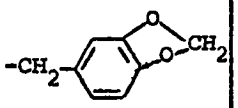
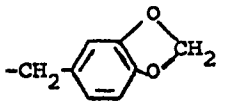
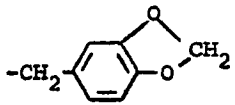
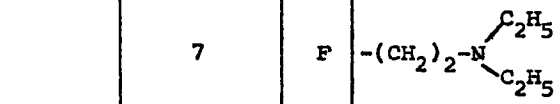
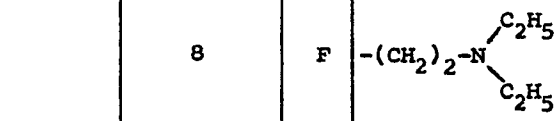
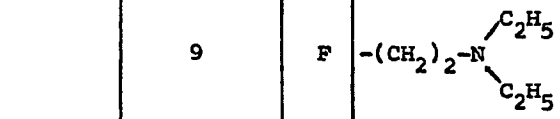
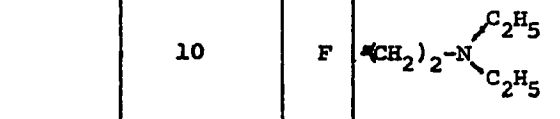
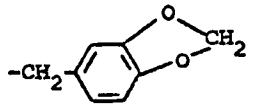
Compound No.	X	R_1	R_2	R_3	Salt prepared	Melting point of salt (°C.)
1	Cl		$-(CH_2)_3-$		maleate (di)	94
2	Cl		$-(CH_2)_3-$		maleate (tri)	190
3	Cl		$-(CH_2)_3-$		hydrochloride (mono)	174
4	F	$-CH_2-CH=CH_2$	$-(CH_2)_3-$		maleate (mono)	134

TABLE II (Cont'd)

Compound No.	X	R_1	R_2	R_3	Salt prepared	Melting point of salt (°C.)
5	F	$-CH_2-CH=CH_2$	$-(CH_2)_3-$		maleate (di)	200
6	F	$-CH_2-C\equiv CH$	$-(CH_2)_3-$		maleate (di)	190
7	F		$-CH_2-$		maleate (di)	105
8	F		$-(CH_2)_2-$		maleate (di)	110
9	F		$-(CH_2)_3-$		maleate (di)	115
10	F		$-(CH_2)_3-$		maleate (tri)	162